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Elizabeth J. Phillips MD, Paul Bigliardi MD, Andreas J. Bircher MD, Ana Broyles MD, Yoon-Seok Chang MD, PhD, Wen-Hung Chung MD, PhD, Rannakoe Lehloenya, Maja Mockenhaupt MD, PhD, Jonny Peter, Munir Pirmohamed MBBS, PhD, Jean-Claude Roujeau MD, Neil Shear MD, Luciana Kase Tanno, Jason Trubiano MBBS, PhD, Rocco Valluzzi MD, Annick Barbaud MD

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CONTROVERSIES IN DRUG ALLERGY: TESTING FOR DELAYED REACTIONS

[1,2]Elizabeth J. Phillips*, MD, [3,]Paul Bigliardi, MD ,[4]Andreas J. Bircher, MD,[5]Ana Broyles, MD, [6]Yoon-Seok Chang,MD, PhD [7]Wen-Hung Chung, MD, PhD,[8]Rannakoe Lehloenya ,[9]Maja Mockenhaupt, MD, PhD, [8]Jonny Peter,[10]Munir Pirmohamed, MBBS, PhD [11]Jean-Claude Roujeau, MD[12]Neil Shear, MD[13,14]Luciana Kase Tanno,[15,16]Jason Trubiano, MBBS, PhD [17]Rocco Valluzzi, MD[18,19]Annick Barbaud, MD*

*The first and last authors EJP and AB were the leaders for this session and manuscript and had equal contributions

[1]Vanderbilt University Medical Center, Nashville, Tennessee, USA[2]Institute for Immunology and Infectious Diseases, Murdoch, Australia, Department of Dermatology, [3]University of Minnesota, Minneapolis, MN, USA, [4]Department of Dermatology, Allergy Unit, University Hospital, University of Basel, Basel, Switzerland,

[5]Boston Children's Hospital and Harvard Medical School, [6]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of Korea, [7]Department of Dermatology, Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospital, Taipei, Linkou and Keelung, Taiwan.[8] Division of Dermatology and Combined Drug Allergy Clinic, Department of Medicine, University of Cape Town, Cape Town, South Africa, [9]Department of Dermatology, Department of Dermatology, Dokumentationszentrum schwerer Hautreaktionen (dZh), Medical Center and Medical Faculty, University of Freiburg, Freiburg, Germany, [10]Centre for Drug Safety Science, Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK, [11]Université Paris-Est Créteil, Créteil, France, [12]Division of Dermatology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada, [13]University Hospital of Montpellier, Montpellier, Sorbonne Université, INSERM, Paris, France, [14]Hospital Sírio Libanês, São Paulo, Brazil, [15]Department of Infectious Diseases and Centre for Antibiotic Allergy and Research, Austin Health, University of Melbourne, Heidelberg, Victoria, Australia, [16]The National Centre for Infections in Cancer, Department of Infectious Diseases, Peter MacCallum Cancer Centre, Parkville, Victoria, Australia, [17]Allergy Department, Pediatric Hospital Bambino Gesù, Rome, Vatican City, Italy, [18]Dermatology and Allergy Department, Tenon Hospital, Medecine Sorbonne University, [19]Assistance publique-hopitaux de Paris, Paris, France

Correspondending author:

Elizabeth J. Phillips, MD, FRCPC, FRACP, FIDSA, FAAAAI

Vanderbilt University Medical Center

1161 – 21st Avenue South, A-2200 Medical Center North

NASHVILLE, TN 37332-2582

(615) 322-9174 (tel); (615) 343-6160

elizabeth.j.phillips@vanderbilt.edu

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Abstract

Controversies exist with regards to *in vivo* approaches to delayed immunologically mediated adverse drug reactions (ADR) such as exanthem (maculopapular eruption), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome/toxic epidermal necrolysis, and fixed drug eruption. In particular, widespread differences exist between regions and practice on the availability and use of intradermal testing (IDT) and patch testing, the standard drug concentrations used, the use of additional drugs in IDT and patch testing to help determine cross-reactivity, the timing of testing in relation to the occurrence of the adverse drug reaction, the use of testing in specific phenotypes, and the use of oral challenge in conjunction with delayed intradermal and patch testing to ascertain drug tolerance. It was noted that there have been advances in the science of delayed T-cell mediated reactions that have shed light on immunopathogenesis and provided a mechanism of pre-prescription screening in the case of HLA-B*57:01 and abacavir hypersensitivity and HLA-B*15:02 and carbamazepine SJS/TEN in Southeast Asians. Future directions should include the collaboration of large international networks to develop and standardize *in vivo* diagnostic approaches such as skin testing and patch testing combined with *ex vivo* and *in vitro* laboratory approaches.

Key words: delayed, intradermal, prick, patch, oral challenge, HLA, AGEP, FDE, DRESS, SJS/TEN

Abbreviations:

ADR Adverse drug reaction

AGEP Acute generalized exanthematous pustulosis

DILI Drug-induced liver injury

DRESS Drug reaction with eosinophilia and systemic symptoms

EAACI European Academy of Allergy and Clinical Immunology

ENDA European Network in Drug Allergy

ESCD European Society of Contact Dermatitis

FDE Fixed drug eruption

HLA Human leukocyte Antigen

IDT Intradermal testing

MPE Maculopapular drug eruption

SDRIFE Symmetrical drug related intertriginous and flexural exanthema

SJS Stevens-Johnson syndrome

TCR T-cell receptor

TEN Toxic epidermal necrolysis

Introduction

Delayed immunologically mediated ADR are defined as those that occur more than 6 hours after dosing (1), with the exception of acute reactions to chemotherapy, which can occur after 6 hours of treatment in patients premedicated with steroids and anti-histamines). Non-life-threatening adverse drug reactions such as delayed exanthem are common and occur in approximately 5% of treatment courses with drugs such as antibiotics, most typically early in the second week of therapy in the case of new sensitization. Regardless of their specific clinical phenotype, delayed immunologically mediated ADR are mostly T-cell mediated; this includes the typical morbilliform as well as urticarial eruptions, and more complicated

and life-threatening reactions such as Stevens Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and single organ diseases such as drug-induced liver and kidney diseases (1). Although the typical way of classifying T-cell mediated reactions has been the revised Gell-Coombs classification, our knowledge of different models by which drugs activate T cells has advanced considerably over the last 10 years (Figure 1 A and B) (2-5). In addition, strong HLA Class I associations between severe T-cell mediated reactions such as abacavir hypersensitivity, SJS/TEN and DRESS that have led to pre-prescription screening strategies (Table 1) (2, 6). It is currently not clear the extent to which exanthems are purely due to parainfectious events to viral or bacterial antigens or stimulation of the immune system by infectious agents with a secondary cutaneous reaction to drugs (7).

Areas of Agreement

Currently, clinical diagnosis is still considered the gold standard for delayed immunologically mediated ADRs but there is general consensus that *in vivo* testing, such as patch testing and/or delayed intradermal testing where sterile preparations of drugs are available, can improve both: (a) the clinical phenotyping of delayed immunologically mediated ADRs, and (b) the ascertainment of the causative drug where the patient is taking multiple drugs started about the same time (8, 9). There is also general agreement that these testing procedures should not be performed for a minimum of 4-6 weeks following the acute reaction to avoid both false positives, false negatives and flare-up of systemic reactions, although published evidence to support any of these is weak (8). For abacavir patch testing, which was also used as a co-primary endpoint in the HLA-B*57:01 testing licensing trial that confirmed the utility of HLA-B*57:01 as a screening test to prevent patch test positive abacavir hypersensitivity, patch tests were described as reliably positive as early as 4 weeks following reactions, and no patients experienced a systemic reaction to patch testing (10, 11). Both patch testing and delayed intradermal testing (IDT) have

also been successfully used to look at potential cross-reactivity between structurally related drugs. For IDT in particular, although there is agreement to use the highest non-irritating concentration of drugs, these concentrations have been defined only with regard to immediate reactions. For IDT for many drugs, the highest non-irritating concentration of the sterile intravenous preparation of drug read after 15-30 minutes may not be similar to that which evokes a T-cell response after 6-24 hours (12, 13). This is particularly true for drugs such as fluoroquinolones and vancomycin which intrinsically cause direct release of histamine, and where the sensitivity of IDT using the lowest concentrations to avoid non-IgE mediated mast cell activation by IDT is very poor (14, 15).

Controversies and differences across regions

The use of IDT and patch testing for diagnosis of delayed immunologically mediated ADRs has been very limited to-date in the United States, and there are currently no supportive guidelines in place. This has been driven by lack of FDA approved reagents for testing and general lack of availability of specialty centers that prepare and compound drugs for intradermal and patch testing (16). The most established experience probably exists in Europe, however clinics practicing these procedures also exist in North America, Asia and Australia amongst others (11, 17-19). There is still a lack of standardized methodological approaches and particularly inconsistency with regards to the drug concentrations (Table 2) (13, 20, 21).

For *in vivo* testing, personal and published evidence suggest that IDT is a more sensitive method than patch testing for reactions such as MPE and may be used when sterile, soluble forms of the drugs are available (8, 22). Increasing evidence supports the safety of IDT skin testing for MPE and DRESS particularly when six or more months has elapsed since the original reaction(8, 23). A questionnaire in 2004 within the European Network in Drug Allergy (ENDA), the Drug Allergy Interest Group of the

European Academy of Allergy and Clinical Immunology (EAACI), showed differences in performing drug allergy investigations (22). Guidelines, such as those by the European Society of Contact Dermatitis (ESCD) and the EAACI, differ in their recommendations (Table 2), making valid comparison of results between centers virtually impossible (13, 20). A position paper providing guidelines on drug concentrations for skin testing was published in 2013, but this paper did not differentiate between the non-irritating concentrations used in skin prick and IDT for immediate testing versus delayed reactions (13). This is particularly relevant as IgE-mediated reactions are less dose-dependent, and mechanistic studies suggest that the activation of T cells by drug and the subsequent interaction with immune receptors occurs largely in a non-covalent and a more dose-dependent fashion (2). At the present time, there is no consensus on the methodology and interpretation of drug IDT. The drug concentration and method used and the criteria for positivity of skin tests all influence the sensitivity and specificity of IDT; consequently, thresholds for specific results may vary between different centers. The most reliable delayed skin test is the IDT, however, delayed positive reactions to prick tests have been described in DRESS, MPE and AGEP, although less frequently (8). Prick testing is carried out on the volar surface of the forearm by putting a drop of drug product or a small amount of powder, then the epidermis is perforated with a special lancet.

Approaches to delayed skin testing differ from that of immediate testing for IgE-mediated reactions where prick testing is still commonly used and results are compared to those obtained with a negative control (0.9% serum saline) and a positive control (histamine). They can be performed with all drugs, however direct histamine releasers such as codeine have to be interpreted with caution. In Europe, for immediate reactions, the recommendation is to perform reading of prick tests at 20 minutes, and at this time the prick test is considered positive if the papule (wheal) is greater than or equal to that measured on the negative control plus 3 millimeters and if there is a surrounding erythema. A prick test has a delayed positive reaction when there is erythema and infiltration at its test location at 24-48 hours (8, 24).

For drug patch tests, in Europe, the method is fairly standardized using commercially available patch test chambers appropriate for the type of vehicle. Patch test tapes typically accommodate solid media such as a drug compound, most commonly dissolved in petrolatum or another vehicle, but occasionally drugs are mixed with water and have to be applied to either a filter paper disk placed in the patch test well or patch test tape with a built in filter. Many academic centers and specialized institutions have responsive pharmacy services that can compound drugs to the highest non-irritating concentration. The stability of many patch test materials has not been validated and is most optimally prepared just before testing. It is also possible to use ready-to-use products in which most drugs are diluted at 10% in petrolatum; unfortunately only a limited number of molecules marketed by Chemotechnique (Velinge, Sweden) are available in some European countries. For certain drugs that are commonly associated with contact reactions such as corticosteroids and neomycin commercially available topical preparations of the drugs are used in patch testing. More recently, a method for compounding drug in the clinic setting by physicians and other providers was described that appeared equivalent to pharmacy prepared and commercially available patch test reagents in sensitivity and specificity (25). In most of the cases, it is necessary to prepare the test material by diluting the drugs in their marketed form.

For drug patch testing, there are numerous recommendations on the dilutions to be used (20, 21). Two sets of European guidelines have been published for clinicians to conduct drug patch tests with the drug in its commercially available form with each drug diluted to 30% (20) or 20% (21) in petrolatum. Ideally, a concentration of 10% of active ingredient should be obtained. Brajon et al. (26) showed that the exact amount of the active ingredient in diluted commercial forms of drugs prepared at 30% in petrolatum varied from 0.05% to 30% and that 25% of the DPTs had an active ingredient's concentration of less than 2%. Testing the drug "as is" on filter paper chambers for non-irritating drugs may show some promise, but further studies are needed. Who performs testing also differs widely across geographical regions. Although there is a lack of published evidence, in the United States, it is uncommon for allergists, immunologists or dermatologists to do drug allergy testing by either prick, IDT or patch testing. This was

supported by a recent survey of Allergy and Immunology program directors in the United States(16). In Europe, dermatologists are more widely available than allergists in many countries and are more likely to perform both patch testing and to a lesser extent delayed IDT (16).

For both delayed IDT and patch testing, it has been recommended that, when possible, corticosteroids and other immunosuppressants are stopped one month prior to testing. The site of patch testing has most commonly been the upper flat part of the back for pragmatic reasons, although this may be the region with the lowest density of resident T cells and the relative sensitivity of the back versus other sites for patch testing is unknown (11, 20). The exception is for fixed drug eruptions (FDE) where the sensitivity is very poor unless the patch test is applied at the site of the previous reaction.

The utility and challenges of *ex vivo* assays such as interferon-γ ELISpot and in vitro assays such as lymphocyte transformation test has been described in detail during the International Drug Allergy Symposium (27). These tests have many of the same challenges as *in vivo* testing with regards to the need for standardization and validation for different drugs and phenotypes. Their negative predictive value is currently not adequate to justify unsupervised rechallenge with potentially implicated drugs in most settings (1, 28). More recent work suggests that combining laboratory based *ex vivo* and/or *in vitro* assays with delayed IDT and patch testing may significantly increase the diagnostic sensitivity (17).

In combination with skin tests when applicable, oral provocation test or challenge test is still considered the gold standard diagnostic procedure for determination of the culprit drug. For immediate reactions, a single or graded dose challenge is considered adequate to exclude an immediate or IgE mediated reaction (29, 30). For delayed reactions in the case of a clear history of a documented benign exanthem, a single dose challenge is considered safe (31). However in the setting of a more remote reaction, it may not be adequate to ascertain tolerance of defined daily doses or a full treatment cycle. A single dose challenge may also be dangerous in the setting of more severe reactions such as severe cutaneous adverse drugs reactions (SCAR) where a single dose has been described to reproduce a reaction particularly in the

setting of a more recent reaction. There is significant lack of consensus for selecting patients who would be appropriate candidates for undergoing oral provocation or challenge following negative delayed IDT or patch testing. For those patients with a history of a mild exanthem and negative delayed patch and/or intradermal testing, it would be common after a tolerated single dose challenge for a 3, 5 or 7 day challenge with an antibiotic such as amoxicillin to be negative. Hence the procedure of multiple day challenge is currently not endorsed and provocation tests lasting several days with antibiotics are debated currently because of the minimal and theoretical risk of inducing antibiotic resistance or sensitization. Other groups have proposed going straight to oral challenge without the previous skin testing step for these benign reactions (30). A caveat to this for delayed reactions and particularly those remote in nature, is that a single dose challenge can be negative and the reaction may potentially be picked up on the second or subsequent doses only. However, the negative predictive value of provocation tests has been reassuring (>90%) for cutaneous adverse drug reactions (32) or beta-lactam antibiotic induced delayed reactions (33, 34). Oral challenge is avoided in the setting of positive IDT or patch tests.

For benign exanthems, there is some evidence to suggest that, in the case of an acute exanthem and if the drug (an antibiotic) is still indicated, it can be continued with at least a temporary clinical tolerance (35). For patients with a history of a benign exanthem who have stopped the drug but require it in the future, there is relative consensus amongst groups for the use of graded reintroduction or a more prolonged desensitization over several hours or days, although the mechanism by which these procedures work is not known. One goal for an international standardization will be to define what a benign delayed exanthem is and under which circumstances the potential inconvenience and symptoms of the rash outweigh the clinical necessity of drug treatment. SCAR and other severe delayed drug reactions such as drug-induced liver injury are generally considered contraindications to rechallenge. In general, if there is an effective alternative drug, the implicated and structurally related drugs should not be reintroduced. Exceptions to this exist in low and middle income countries where diseases of high global burden, such as HIV and tuberculosis, demand complex treatment regimens and where immunologically-mediated ADRs

may significantly restrict treatment options (1). In these cases, where the risk of morbidity and mortality from the underlying disease outweighs or at least equals the risk of morbidity and mortality from the drug reaction, the risk/benefit ratio sways towards sequential rechallenge of potentially implicated drugs. The availability of *in vivo* and *ex vivo* testing to guide rechallenge choices would be extremely helpful in these settings.

Significant knowledge gaps still exist in terms of use of combinations of genetic, *in vivo* skin testing and *ex vivo*/*in vitro* diagnostic testing for delayed reactions. Given the lack of 100% negative predictive value of any one diagnostic approach, combined approaches are likely to be necessary. In addition, much like the knowledge gaps that exist in the treatment of SCAR, advances in knowledge of the immunopathogenesis will drive the discovery of both therapeutic and diagnostic targets.

Consensus Recommendations and Future Directions

- There is a need for additional evidence and standardization of approaches to the diagnosis of delayed immunologically mediated ADR in multicenter studies and potential opportunities to incorporate this into treatment intervention studies.
- Standardization of clinical diagnosis is important to studies looking at the efficacy of diagnostic approaches to delayed immunologically mediated ADR.
- A consensus committee should focus on standardization of procedures for the most common drugs and phenotypes with the highest yield that will have the most clinical impact.
- Current literature supports the use of patch testing and delayed IDT in specific phenotypes (table 3).
- The highest utility of *in vivo* testing approaches will be the combination of exemplary phenotype standardization with *ex vivo* and *in vitro* laboratory based testing (27); however a greater evidence

base is needed for not only what combinations of tests to use but when to perform testing following an acute reaction.

- For *in vivo* testing for delayed reactions, and in particular for delayed IDT, there is a need for harmonization of approaches, study of and standardization of drug concentrations, vehicles, preparation and knowledge on stability of test solutions.
- Given the rarity of SCAR, large collaborative networks are needed to study the sensitivity, specificity and safety of IDT and patch testing in these populations, as well as validating the approach such as optimal time since reaction to testing, concentration of drugs and/or metabolites and the utility of these approaches, particularly when combined with ex vivo and in vitro testing in ascertaining the implicated drug, potential cross-reactive drugs and safe future drug choices.
- Additional scientific advances into knowledge of immunopathogenesis of these reactions may answer many key questions and will drive strategies for improved prevention, diagnosis and treatment.

275 Table 1: HLA Associations with Delayed IM-ADR and Implications for Translation
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277 Table 1: Recently Described HLA Associations with Delayed Drug Reactions

Drug Phenotype	HLA Allele	HLA Risk Allele Prevalence	Disease Prevalence	OR	NPV	PPV	NNT	Current Use as Screening Test
Abacavir **Hypersensitivity Syndrome(2, 10, 36)**	B*57:01	5-8% European ancestry <1% African/Asia 2.5% African American	8% (3% true HSR and 2-7% false positive diagnosis	960	100% for patch test confirmed	55%	13	Routine in HIV clinical practice in developed world
Allopurinol **SJS/TEN and DRESS/DIHS(2, 37, 38)**	B*58:01	9-11% Han Chinese 1-6% European ancestry[#]	1/250-1/1000	580	100% (Han Chinese, Southeast Asian)[*]	3%	250	Selectively used[^]
Carbamazepine **SJS/TEN(2, 39)**	B*15:02[#]	10-15% Han Chinese <1% Koreans, Japanese <0.1% European Ancestry	1-4% (Han Chinese)	>1000	100% (Han Chinese, East Asian)	3%	1000	Routine in many Southeast Asian countries

Dapsone **DRESS/DHIS(2, 40)**	B*13:01	2-20% Chinese 28% Papuans/Australian Aboriginals 0% European/African 1.5% Japanese <2% African and African American	1-4% Han Chinese	20	99.8% (Han Chinese, East Asian)	7.8%	84	Screening programs implemented in China and Southeast Asia where leprosy prevalent
Flucloxacillin(41)	B*57:01	5-8% European ancestry <1% African/Asia 2.5% African American	8.5/100,000	81	99.99	0.14 %	13819	No

NNT = Number needed to test to prevent one case of disease; [+]other alleles of B75 serotype (HLA-B*15:21, B*15:11; B*15:08

[*]From RegiSCAR data approximately 60% of Europeans with allopurinol SJS/TEN carry HLA-B*58:01 and HLA risk alleles other than HLA-B*58:01 are thought to be relevant in those of European and African origin; [^]may have increased utility in patients at higher risk with renal insufficiency and because of high cost of alternatives (febuxostat) and low positive predictive value adoption has varied.[#]HLA-B*15:02 is associated with SJS/TEN in Southeast Asians but not DRESS or MPE. HLA-A*31:01 is more prevalent in Europeans and Japanese associated with carbamazepine DRESS and MPE and prospective evidence for decreased SCAR with HLA-A*31:01 screening in Japanese(42-44).

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Table 2: Comparison of international guidelines published for performing delayed intradermal tests

	ESCD (14)	EAACI (15)
Volume injected	0.04 ml (in saline or phenolated saline)	0.02 to 0.05 ml
Criteria for delayed positivity	Papule at 24h	24-72 h infiltrated erythema
Site	Volar aspect of forearm or extensor aspect of upper arm	Volar aspect of the forearm (or other regions)
Negative control with saline	Yes	Yes
Positive control specific for delayed response	No	No

ESCD: European Society of Contact Dermatitis, EAACI : European Academy of Allergy and Clinical Immunology

294 Table 3: Use of Delayed Prick/Intradermal, Patch Testing and Systemic Provocation for Delayed
295 Reactions (8, 9, 23, 24)[+]

	Patch tests*	Prick tests	IDT[^]	Systemic Provocation
Maculopapular rash	Useful (positive in 10-40%)	Potentially useful	Potentially useful however direct oral provocation maybe indicated in low probability situations	After negative skin tests with delayed readings in low probability situations. NPV of 90%.
Generalized eczema (Contact reaction)	Useful	Potentially useful	Potentially useful	After negative delayed skin test with delayed readings. NPV is unknown
Baboon syndrome or SDRIFE	Useful (positive in 52-82%)	Potentially useful	Potentially useful	After negative skin tests with delayed readings. NPV is unknown
Fixed drug eruption	Useful with in situ application in area of previous reaction (up to 40% positive)	Unknown	Unknown	At full dose when patch tests or repeated application tests are negative. NPV is unknown.
Photosensitization	Photopatch tests with a 5 joule exposure to UVA, Irradiation at 48 h.	No value	No value	No value without exposure to UV
Acute generalized exanthematous pustulosis	Useful – sensitivity depends on the specific implicated drug (up to 58%)	Unknown	Potentially useful	Systemic provocation of suspected drug or cross-reactive drugs is contraindicated.
DRESS	Useful (positive in 32-64%) dependent on drug Advised 6 months after	Described delayed positive at 24 hours but unknown utility	Delayed reading at 24 hours Currently unknown safety	Systemic provocation with the highly suspected drug and cross-

	disappearance of rash and other sequelae			reactive drugs contraindicated.
SJS/TEN	Low sensitivity (<30%). Can be considered if there is benefit of diagnostic information obtained[#]	Considered contraindicated	Considered contraindicated	Systemic provocation with the suspected drug is contraindicated.
Drug-induced liver disease (or another single organ phenotype)	Low sensitivity if no cutaneous involvement	Low sensitivity if no cutaneous involvement	Low sensitivity if no cutaneous involvement	Systemic provocation with the suspected drug is contraindicated.

**initial read at 48 hours; reading at 72, 96 hours and 1 weeks if initial negative; [^]read at 48 hours if 24 hours negative.[+]Practices differ significantly between the United States and Europe and parts of Asia at this time. In Europe both allergists and dermatologists perform both skin testing, patch testing and systemic provocation. In the US allergists perform mainly skin testing and oral provocation and there are few canters where delayed testing is offered. Drug patch testing and delayed IDT is not frequently offered in the United States by either allergists or dermatologists and is offered in select centers only.[#]For allopurinol and its metabolite oxypurinol patch testing has had 0% sensitivity.*

Figure Legends

Figure 1. **A. Extended Gell & Coombs Classification of Delayed T-cell mediated adverse drug reactions**. AGEP, acute generalized exanthematous pustulosis; CTL, cytotoxic T lymphocyte; CXCL8, chemokine 8; GM-CSF granulocyte-macrophage colony stimulating factor; IFN-γ (interferon-γ); IL-interleukin, PMN, polymorphonuclear neutrophil, DRESS, drug reaction with eosinophilia and systemic symptoms; Stevens-Johnson Syndrome/Toxic epidermal necrolysis (SJS/TEN); Th1, helper T cell type 1; Th2, helper T cells type2: TNF-α, tumor necrosis factor-α,(adapted from Pichler et al). Frames below show representative clinical pictures: IVa (positive delayed intradermal to 1% lidocaine in patient with

contact reaction to lidocaine (L) without demonstrable cross-reactivity to mepivacaine (C), IVb (maculopapular exanthem); IVc (TEN); IVd (AGEP)

B. **Proposed mechanisms of T-cell mediated reactions including the hapten/prohapten model, the pharmacological-interaction model and the altered peptide repertoire model** that provide a proposed model for how drugs activate T cells. The hapten-prohapten model shows the drug covalently binds to a peptide either intracellularly in the endoplastic reticulum prior to peptide processing and presentation or at the cell surface The pharmacological interaction model (p-i) shows the drug non-covalently binding to the HLA-molecule and/or T-cell receptor to result in direct T-cell activation. The altered peptide repertoire model shows a drug binding non-covalently in the HLA antigen binding cleft that alters the repertoire of self-peptide ligands leading to presentation of novel peptide ligands that are recognized as foreign and elicit an immune response. TCR – T-cell receptor.

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References:

1. Peter JG, Lehloenya R, Dlamini S, Risma K, White KD, Konvinse KC, et al. Severe Delayed Cutaneous and Systemic Reactions to Drugs: A Global Perspective on the Science and Art of Current Practice. J Allergy Clin Immunol Pract. 2017;5(3):547-63.

2. White KD, Chung WH, Hung SI, Mallal S, Phillips EJ. Evolving models of the immunopathogenesis of T cell-mediated drug allergy: The role of host, pathogens, and drug response. J Allergy Clin Immunol. 2015;136(2):219-34; quiz 35.

3. Ostrov DA, Grant BJ, Pompeu YA, Sidney J, Harndahl M, Southwood S, et al. Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire. Proc Natl Acad Sci U S A. 2012;109(25):9959-64.

4. Illing PT, Vivian JP, Dudek NL, Kostenko L, Chen Z, Bharadwaj M, et al. Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. Nature. 2012;486(7404):554-8.

5. Pavlos R, White KD, Wanjalla C, Mallal SA, Phillips EJ. Severe Delayed Drug Reactions: Role of Genetics and Viral Infections. Immunol Allergy Clin North Am. 2017;37(4):785-815.

6. Garon SL, Pavlos RK, White KD, Brown NJ, Stone CA, Jr., Phillips EJ. Pharmacogenomics of off-target adverse drug reactions. Br J Clin Pharmacol. 2017;83(9):1896-911.

7. Abana CO, Pilkinton MA, Gaudieri S, Chopra A, McDonnell WJ, Wanjalla C, et al. Cytomegalovirus (CMV) Epitope-Specific CD4(+) T Cells Are Inflated in HIV(+) CMV(+) Subjects. J Immunol. 2017;199(9):3187-201.

8. Barbaud A, Collet E, Milpied B, Assier H, Staumont D, Avenel-Audran M, et al. A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. Br J Dermatol. 2013;168(3):555-62.

9. Barbaud A. Skin testing in delayed reactions to drugs. Immunol Allergy Clin North Am. 2009;29(3):517-35.

10. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008;358(6):568-79.

11. Phillips EJ, Sullivan JR, Knowles SR, Shear NH. Utility of patch testing in patients with hypersensitivity syndromes associated with abacavir. AIDS. 2002;16(16):2223-5.

12. Empedrad R, Darter AL, Earl HS, Gruchalla RS. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. J Allergy Clin Immunol. 2003;112:629-30.

13. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2013;68(6):702-12.

14. McNeil BD, Pundir P, Meeker S, Han L, Undem BJ, Kulka M, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. Nature. 2015;519(7542):237-41.

15. Azimi E, Reddy VB, Lerner EA. Brief communication: MRGPRX2, atopic dermatitis and red man syndrome. Itch (Phila). 2017;2(1).

16. Derrick MI, Williams KB, Shade LMP, Phillips EJ. A survey of drug allergy training opportunities in the United States. J Allergy Clin Immunol Pract. 2018;6(1):302-4.

17. Trubiano JA, Strautins K, Redwood AJ, Pavlos R, Konvinse KC, Aung AK, et al. The Combined Utility of Ex vivo IFN-gamma Release Enzyme-Linked ImmunoSpot Assay and In vivo Skin Testing in Patients With Antibiotic-Associated Severe Cutaneous Adverse Reactions. J Allergy Clin Immunol Pract. 2017.

18. Lin YT, Chang YC, Hui RC, Yang CH, Ho HC, Hung SI, et al. A patch testing and cross-sensitivity study of carbamazepine-induced severe cutaneous adverse drug reactions. J Eur Acad Dermatol Venereol. 2013;27(3):356-64.

19. Phillips E, Knowles SR, Weber EA, Blackburn D. Cephalexin tolerated despite delayed aminopenicillin reactions. Allergy. 2001;56(8):790.

20. Barbaud A, Goncalo M, Bruynzeel D, Bircher A, European Society of Contact D. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. Contact Dermatitis. 2001;45(6):321-8.

21. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy. 2002;57(1):45-51.

22. Gomes E PW, Demoly P, Aberer W, Frew A, de Weck A, Ballmer-Weber, BK, Barbaud A, Bilo B, Bircher A, Birnbaum J,. Blanca M, Blomecke B, Brockhow K, Campi P, Dzviga C, Drouet M, Eberlein-Konig B, Fernandez J, Fuchs T et al. The drug ambassador project - the diversity of diagnostic procedures for drug allergy around Europe. Allergy and Clinical Immunology International. 2005;17(1):9-18.

23. Trubiano JA, Douglas AP, Goh M, Slavin MA, Phillips EJ. The Safety of Antibiotic Skin Testing in Severe T-cell-Mediated Hypersensitivity of immunocompetent and immunocompromised hosts. J Allergy Clin Immunol Pract. 2018.

24. Barbaud A. Skin testing and patch testing in non-IgE-mediated drug allergy. Curr Allergy Asthma Rep. 2014;14(6):442.

25. Assier H, Valeyrie-Allanore L, Gener G, Verlinde Carvalh M, Chosidow O, Wolkenstein P. Patch testing in non-immediate cutaneous adverse drug reactions: value of extemporaneous patch tests. Contact Dermatitis. 2017;77(5):297-302.

26. Brajon D, Menetre S, Waton J, Poreaux C, Barbaud A. Non-irritant concentrations and amounts of active ingredient in drug patch tests. Contact Dermatitis. 2014;71(3):170-5.

27. Mayorga C ED, Lang DM, Pichler WJ, Sabato V, Park MA, Makowska J, Atanakovic-Markovic M, Bonadonna P, Jares E. Controversies in drug allergy: in vitro testing. J Allerg Clin Immunol. 2018.

28. Mayorga C, Celik G, Rouzaire P, Whitaker P, Bonadonna P, Rodrigues-Cernadas J, et al. In vitro tests for drug hypersensitivity reactions: an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2016;71(8):1103-34.

29. Joint Task Force on Practice P, American Academy of Allergy A, Immunology, American College of Allergy A, Immunology, Joint Council of Allergy A, et al. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010;105(4):259-73.

30. Mill C, Primeau MN, Medoff E, Lejtenyi C, O'Keefe A, Netchiporouk E, et al. Assessing the Diagnostic Properties of a Graded Oral Provocation Challenge for the Diagnosis of Immediate and Nonimmediate Reactions to Amoxicillin in Children. JAMA Pediatr. 2016;170(6):e160033.

31. Lammintausta K, Kortekangas-Savolainen O. Oral challenge in patients with suspected cutaneous adverse drug reactions: findings in 784 patients during a 25-year-period. Acta Derm Venereol. 2005;85:491-6.

433 32. Waton J, Pouget-Jasson C, Loos-Ayav C, Trechot P, Bursztejn AC, Schmutz JL, et al.
434 Drug re-challenges in cutaneous adverse drug reactions: information and effectiveness in the
435 long-term management of patients. Allergy. 2011;66:941-7.

436 33. Demoly P, Romano A, Botelho C, Bousquet-Rouanet L, Gaeta F, Silva R, et al.
437 Determining the negative predictive value of provocation tests with beta-lactams. Allergy.
438 2010;65(3):327-32.

439 34. Tonson la Tour A, Michelet M, Eigenmann PA, Caubet JC. Natural History of Benign
440 Nonimmediate Allergy to Beta-Lactams in Children: A Prospective Study in Retreated Patients
441 After a Positive and a Negative Provocation Test. J Allergy Clin Immunol Pract.
442 2018;6(4):1321-6.

443 35. Trautmann A, Benoit S, Goebeler M, Stoevesandt J. "Treating Through" Decision and
444 Follow-up in Antibiotic Therapy-Associated Exanthemas. J Allergy Clin Immunol Pract.
445 2017;5(6):1650-6.

446 36. Saag M, Balu R, Phillips E, Brachman P, Martorell C, Burman W, et al. High sensitivity
447 of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir
448 hypersensitivity in white and black patients. Clin Infect Dis. 2008;46(7):1111-8.

449 37. White KD, Abe R, Ardern-Jones M, Beachkofsky T, Bouchard C, Carleton B, et al.
450 SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation. J Allergy
451 Clin Immunol Pract. 2018;6(1):38-69.

452 38. Chen DY, Chen YM, Tsai WC, Tseng JC, Chen YH, Hsieh CW, et al. Significant
453 associations of antidrug antibody levels with serum drug trough levels and therapeutic response
454 of adalimumab and etanercept treatment in rheumatoid arthritis. Ann Rheum Dis.
455 2015;74(3):e16.

456 39. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, et al. Medical genetics: a
457 marker for Stevens-Johnson syndrome. Nature. 2004;428(6982):486.

458 40. Zhang FR, Liu H, Irwanto A, Fu XA, Li Y, Yu GQ, et al. HLA-B*13:01 and the dapsone
459 hypersensitivity syndrome. N Engl J Med. 2013;369(17):1620-8.

460 41. Daly AK, Donaldson PT, Bhatnagar P, Shen Y, Pe'er I, Floratos A, et al. HLA-B*5701
461 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. Nat Genet.
462 2009;41(7):816-9.

463 42. Phillips EJ, Sukasem C, Whirl-Carrillo M, Muller DJ, Dunnenberger HM, Chantratita W,
464 et al. Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and
465 Use of Carbamazepine and Oxcarbazepine: 2017 Update. Clin Pharmacol Ther.
466 2018;103(4):574-81.

467 43. McCormack M, Alfirevic A, Bourgeois S, Farrell JJ, Kasperaviciute D, Carrington M, et
468 al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J
469 Med. 2011;364(12):1134-43.

470 44. Mushiroda T, Takahashi Y, Onuma T, Yamamoto Y, Kamei T, Hoshida T, et al.
471 Association of HLA-A*31:01 Screening With the Incidence of Carbamazepine-Induced
472 Cutaneous Adverse Reactions in a Japanese Population. JAMA Neurol. 2018;75(7):842-9.

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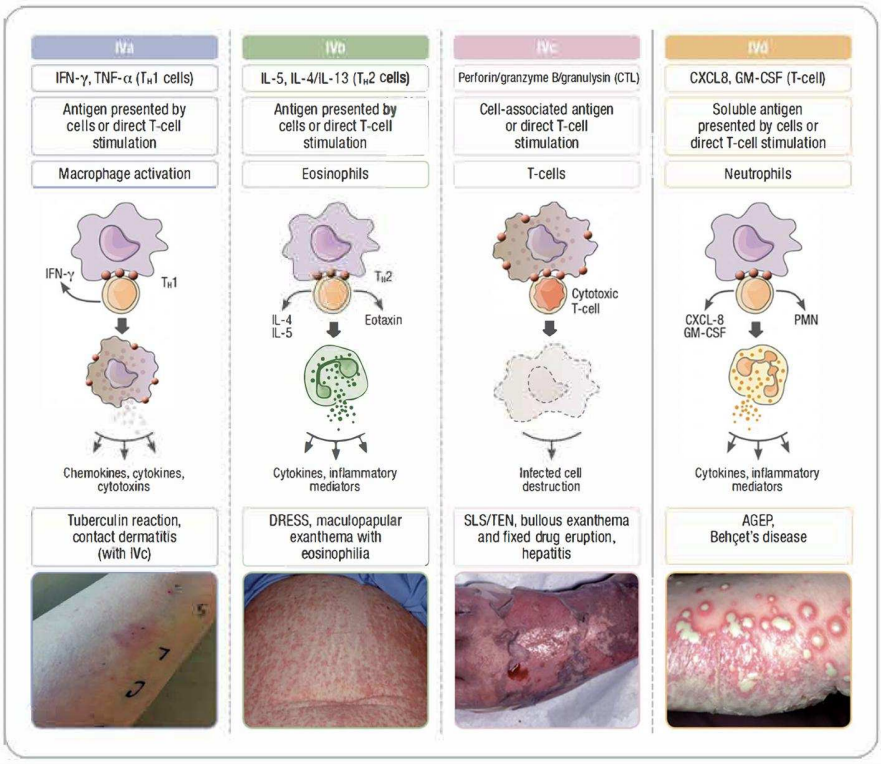
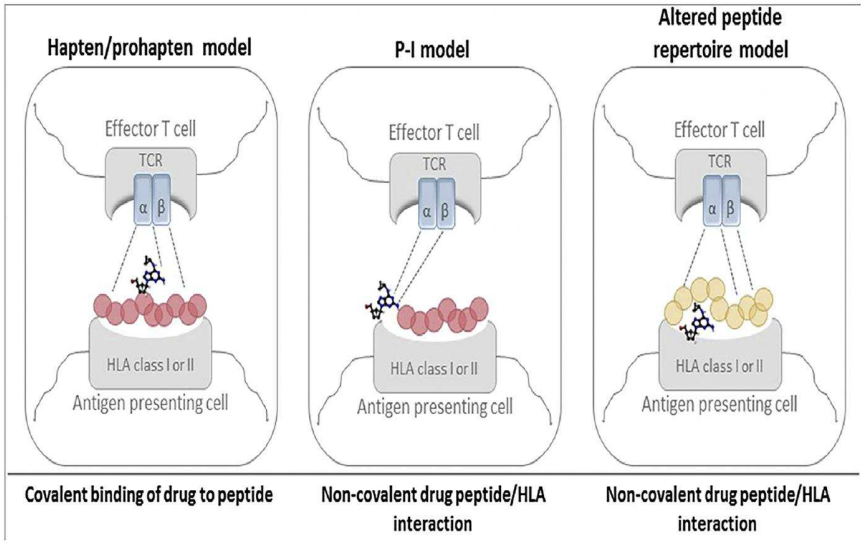
A.


IVa
IFN-γ, TNF-α (T_H1 cells)
Antigen presented by cells or direct T-cell stimulation
Macrophage activation
IFN-γ
T_H1
Chemokines, cytokines, cytotoxins
Tuberculin reaction, contact dermatitis (with IVc)
IVb
IL-5, IL-4/IL-13 (T_H2 cells)
Antigen presented by cells or direct T-cell stimulation
Eosinophils
T_H2
IL-4
IL-5
Eotaxin
Cytokines, inflammatory mediators
DRESS, maculopapular exanthema with eosinophilia
IVc
Perforin/granzyme B/granulysin (CTL)
Cell-associated antigen or direct T-cell stimulation
T-cells
Cytotoxic T-cell
Infected cell destruction
SLS/TEN, bullous exanthema and fixed drug eruption, hepatitis
IVd
CXCL8, GM-CSF (T-cell)
Soluble antigen presented by cells or direct T-cell stimulation
Neutrophils
CXCL-8
GM-CSF
PMN
Cytokines, inflammatory mediators
AGEP, Behçet's disease

B.



Neo-epitope formed by drug binding to peptide	Drug bind to peptide/ HLA at cell surface	Drug binding results In a change in HLA binding motif and a selection of altered peptides